**Review Article**

**Systematic Implementation of Quality by Design (QbD): A Perspective from Generic Pharmaceutical Industries**

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**ABSTRACT**

Quality by Design (QbD) is a structured approach to pharmaceutical development that ensures predefined product quality by understanding and controlling manufacturing processes from the outset. Unlike traditional methods focusing on end-product testing, QbD emphasizes building quality into the product design itself, enhancing manufacturing efficiency and regulatory compliance.

This review highlights the application of QbD in developing generic solid oral drug products, emphasizing tools like risk assessment, process design, and control strategies to achieve consistent quality. Key components include identifying and managing Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical Material Attributes (CMAs), which influence formulation, process development, and overall performance. The integration of Design of Experiments (DoE) and effective control strategies are also discussed. Addressing regulatory expectations, particularly those from the International Council for Harmonisation (ICH), this review outlines how QbD principles help generics meet bioequivalence standards, ensuring consistent quality and performance. Applying QbD not only enhances product robustness and manufacturing efficiency but also improves patient safety through better process understanding and continuous improvement.

# INTRODUCTION

In recent decades, the pharmaceutical industry has faced challenges in quality assurance and regulatory compliance, highlighting the need for structured approaches to development. Historically, fixed manufacturing processes and extensive testing were maintained product quality. However, the limitations of the Quality by Test (QbT) approach have become evident. Under QbT, materials and products failing to meet specifications must be discarded. This approach's lack of process understanding often results in unrecognized variability, leading to inconsistent quality, batch rejections, low patient acceptance, and increased costs (Simões, Veiga, & Vitorino, 2024). Any changes to the formulation composition or manufacturing process require a lengthy and costly post-approval change submission (L. X. Yu, 2008; Zhang & Mao, 2017).

In the context of Quality by Design (QbD), Dr. Janet Woodcock emphasizes that “Product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches”(Woodcock, 2004) this statement aligns perfectly with the fundamental principle of QbD "Quality cannot be tested into the product; it must be designed into it." Quality by Design (QbD) is a systematic approach to pharmaceutical development, involving the design and development of formulations and manufacturing processes to ensure predefined product quality. According to ICH Q8, QbD (Quality by Design) is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on

sound science and quality risk management (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009). QbD implementation into the pharmaceuticals product development reducing post-approval changes(Pramod, Tahir, Charoo, Ansari, & Ali, 2016) .

The concept of Quality by design (QbD) is mentioned in ICH Q8 guidance. The fundamental principle of QbD is that "Quality cannot be tested into the product; it must be designed into it.". Quality by Design (QbD) is a systematic approach to pharmaceutical development, involving the design and development of formulations and manufacturing processes to ensure predefined product quality. Implementing QbD transforms the chemistry, manufacturing, and control (CMC) review of generic products into a science-based pharmaceutical quality assessment (L. X. Yu, 2008).

According to ICH Q8 (Quality by Design), QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009). The pharmaceutical industry knows the product's quality, safety and effectiveness. Product quality has increased by implementing QbD scientific tools (Rathore, 2009).

The FDA's emphasis on Quality by Design (QbD) stems from recognizing that more extensive testing does not inherently improve product quality—a principle well-established in other industries. The following equation(Lionberger, Lee, Lee, Raw, & Yu, 2008) highlights the foundation of quality:

**Pharmaceutical Quality = f (drug substance, excipients, manufacturing, packaging)**

Improving quality requires embedding it directly into the product. This is achieved by gaining a comprehensive understanding of how formulation and manufacturing process variables influence product quality, as represented by the function in the equation.

The goal of pharmaceutical development is to create a quality product and a manufacturing process that consistently achieves the desired performance. Regardless of the circumstances, products should be designed to satisfy patients' needs and deliver the intended performance. Development strategies differ between companies and products, with varying approaches and extents of development that should be detailed in the submission. An applicant may opt for an empirical approach, a systematic approach, or a combination of both for product development.

The Food and Drug Administration (FDA) (Nasr, 2013; Woodcock, 2004; L. Yu, 2013) and the pharmaceutical industry (Ganzer, Materna, Mitchell, & Wall, 2005; Glodek et al., 2006) are discussing Quality by Design (QbD).

From available USFDA database, Quality by design for ANDA: An example for Immediate-release dosage form (U.S. Food and Drug Administration (FDA), April 2012) and An example of Modified Release dosage form(U.S. Food and Drug Administration (FDA), December 2011), this review article explains steps for QbD implementation in generic solid oral product.

# STEP BY STEP QBD IN GENERIC DRUG PRODUCT

Below sub-subsections outline the methodology for applying QbD principles in the development of a generic solid oral drug product.

## Analysis of The Brand Product

A detailed outline for the Reference Listed Drug (RLD) analysis is to be performed as follows.

* **Clinical :**
* **Therapeutic Indication**: This refers to the specific disease or condition that the drug is intended to treat.
* **Mechanism of Action**: This describes how the drug works at a molecular level to produce its therapeutic effect.
* **Immediate Release or Extended Release:** Immediate-release (IR) formulations release the active ingredient quickly, while extended-release (ER) formulations release it slowly over time.
* **Dosing Frequency:** This indicates how often the drug should be taken, such as "once daily" or "twice daily."
* **Number of Strengths:** This refers to the different dosages available for the drug, like 5 mg, 10 mg, and 20 mg.
* **Reference Standard for Bioequivalence Studies:** This is the strength and formulation used as a benchmark in bioequivalence studies to ensure generics are equivalent to the brand-name drug.
* **Score or Un-score Tablets:** Scored tablets have a line or notch to help split them into smaller doses, while unscored tablets do not.
* **Label Warning for Potential Risk of Dose Dumping When Consumed with Alcohol:** This is a warning that should be included if consuming the drug with alcohol can lead to a rapid release of the drug, potentially causing adverse effects.
* **Pharmacokinetics :**
* **Tmax (Time to Maximum Concentration):** This is the time it takes for the drug to reach its highest concentration in the bloodstream after administration.
* **Cmax (Maximum Concentration):** This is the highest concentration of the drug in the bloodstream.
* **AUC (Area Under the Curve):** This represents the total drug exposure over time, essentially the integral of the concentration-time curve.
* **Elimination Half-Life:** This is the time it takes for the concentration of the drug in the bloodstream to be reduced by half.

These parameters help in understanding the drug's absorption, distribution, metabolism, and excretion (ADME) properties

* **Drug Release :** Drug release in FDA-recommended media (if available) as well as in various dissolution media for both whole and split tablets (if available) to be performed f
* **Physicochemical Characterization :**
* **Description:** Detailed appearance and physical attributes of the product.
* **Batch Number:** Unique identifier for the specific production batch.
* **Expiry Date:** The date until which the product is expected to remain effective and safe for use.
* **Strength:** The amount of active ingredient per dosage form (e.g., 50 mg, 100 mg).
* **Average Tablet Weight:** The mean weight of a single tablet.
* **Score/Unscore:** Indicates whether the tablet has a line for splitting.
* **Coated/Uncoated:** Specifies if the tablet has a coating or not.
* **Diameter:** The width of the tablet, usually measured in millimeters.
* **Thickness:** The height of the tablet, usually measured in millimeters.
* **Hardness:** The force required to break the tablet, measured in kP or Newtons.
* **Disintegration Time:** For immediate-release tablets, the time taken for the tablet to break down into smaller fragments in a specified liquid medium.
* **Assay:** The measurement of the active ingredient content within the tablet.
* **Related Compounds:** Analysis of impurities and degradation products that may be present.
* **Composition :** Identify the qualitative RLD composition based on the brand product labeling, and the quantitative RLD composition based on patent literature and reverse engineering

## Quality Target Product Profile

The quality target product profile (QTPP) is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009).

Considering the clinical and pharmacokinetic (PK) properties, along with the in vitro dissolution and physicochemical characteristics of the brand product, a QTPP should be established for the generic dosage form. The following aspects should be targeted based on the brand product:

* Dosage form
* Dosage design
* Route of administration
* Dosage strength
* Pharmacokinetics
* Stability
* Container closure system
* Administration/Concurrence with labeling
* Drug product Critical Quality Attributes (CQA)

## Critical Quality Attributes

A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009). Determining a CQA from the QTPP involves assessing the potential harm to a patient if the product exceeds the acceptable range for that attribute. The following CQAs should be targeted, considering safety and efficacy:

* **Assay**: Ensures the correct potency of the drug in the dosage form.
* **Content Uniformity**: Ensures each dosage unit contains the intended amount of drug substance.
* **Dissolution**: Ensures the drug is released at the intended rate in the body.
* **Degradation Products**: Specifies acceptable levels of impurities and degradation products to ensure safety.

## Dissolution Method Development

The biopharmaceutics drug classification system seeks to establish a connection between in vitro drug product dissolution and in vivo bioavailability. It highlights that drug dissolution and gastrointestinal permeability are key factors determining the rate and extent of drug absorption. This classification system provides recommendations for establishing standards for in vitro drug dissolution testing methods that align with in vivo processes. These methods must be based on the physiological and physicochemical factors that influence drug absorption. The analysis identifies situations where in vitro-in vivo correlation may not be expected, such as for rapidly dissolving drugs with low permeability. It also suggests that for very rapidly dissolving drugs with high solubility (e.g., 85% dissolution within 15 minutes), a simple one-point dissolution test may be sufficient to ensure bioavailability. Conversely, for slowly dissolving drugs, a detailed dissolution profile with multiple time points is necessary, incorporating conditions such as low pH, physiological pH, and surfactants to simulate in vivo processes (Amidon, Lennernäs, Shah, & Crison, 1995).

Understanding the relationship between in vitro drug release and in vivo performance is essential for several reasons:

* Assessing the impact of formulation and process variable changes on drug product quality during development.
* Predicting the performance of commercial batches using bioequivalence data from the exhibit batch.
* Facilitating the evaluation of post-approval changes.

To achieve this, a predictive dissolution method should be developed to establish an in vitro-in vivo relationship (IVIVR) that links in vitro drug release with in vivo performance. This predictive dissolution method should accurately forecast the in vivo performance of the drug product and distinguish between formulations with different performance characteristics.

Moreover, the dissolution method must be discriminative to effectively detect differences in the performance of drug products(U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Guidance for Industry, August 1997). A discriminative dissolution method helps identify any variations in the formulation or manufacturing process that could impact the drug's release performance(Ashokraj et al., 2016). For immediate release dosage form, dissolution method to be developed based on drug substance aqueous solubility and absorption window.

For modified-release dosage forms, the effectiveness of the dissolution method in predicting performance for both brand and generic drug products will be assessed by:

* Testing at various pH levels (e.g., water, 0.1 N HCl, pH 4.5 phosphate buffer, and pH 6.8 phosphate buffer) to evaluate the pH-dependent solubility of the drug substance and the behavior of the extended-release polymer at different pH levels.
* Using different volumes of dissolution medium (e.g., 250 mL, 500 mL, 900 mL) to determine the impact of medium volume on the dissolution rate.
* Testing at different stirring speeds (e.g., 25 rpm, 50 rpm, 75 rpm) while ensuring that coning does not occur at low speeds during dissolution testing.
* Employing different USP apparatus (e.g., Apparatus I [Basket]Ae, Apparatus II [Paddle], Apparatus III [Reciprocating Cylinder]).

During these evaluations, one variable will be altered at a time, keeping all other variables constant, to assess the predictive power of the dissolution method.

After establishing discriminating dissolution conditions, the subsequent step will be to assess whether any of these conditions can reasonably predict the in vivo performance of the drug product.

## Pilot Bioequivalence Study

Pilot bioequivalence (BE) studies are invaluable to demonstrate that the *in vitro* dissolution used is appropriate. For modified release dosage form, Establishing an IVIVC (*in vitro-in vivo* correlation) is one of the more robust methods to ensure the continued bioequivalence (BE) of commercial lots. It provides control over post-approval changes to critical material attributes (CMAs) and critical process parameters (CPPs), thus maintaining consistent product quality and BE. However, establishing an IVIVC can be challenging. A product designed and developed using QbD principles should result in the establishment of a predictive *in vitro* dissolution method. Although less robust than an IVIVC, establishing a predictive *in vitro* dissolution method may be sufficient to ensure product quality when combined with a thorough understanding of the product and process. Additionally, such an *in vitro* method will be valuable for assessing post-approval changes. It is well acknowledged that an extended-release product developed at the pivotal batch scale may not always scale up to commercial scale and yield a drug product that is bioequivalent (BE) to the Reference Listed Drug (RLD). Both fed and fasting bioequivalence studies may be necessary to ensure that the commercial batches are BE to the RLD. It is also expected that the risk assessment of a product developed using Quality by Design (QbD) principles will identify all Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) and include adequate controls; one of these controls will be a discriminating in vitro method. While the bioequivalence study of commercial batches will ensure the BE of the drug product, a discriminating in vitro method will assure product quality throughout its lifecycle (including post-approval changes).

The 90% confidence Interval meets the bioequivalence threshold of 80-125% for Cmax and AUC under fasted, fed, and other conditions as specified in the product-specific guidance for the brand product (U.S. Food and Drug Administration (FDA) Draft Guidanace, August 2021).

## Component of Drug Product

Drug substances and excipients are components of drug products.

The assessment of various physical properties of the drug substance, such as appearance, particle morphology, particle size distribution (d10, d50, d90), and solid-state form (including the polymorphic form and its stability in the final drug product), this should be conducted using XRPD by comparing the spectra of the drug substance, drug product, and individual excipients. Additionally, properties such as melting point, solubility in different pH environments, hygroscopicity, density, and flow characteristics should also be evaluated. Chemical properties such as pKa and the stability of the drug substance in both solid state and solution, as well as biological properties like partition coefficient, Caco-2 permeability, and biopharmaceutical classification, should also be assessed. A risk assessment of drug substance critical attributes is essential for ensuring the quality and safety of a drug product.

**Solid-state form :** The solid-state form of a drug substance refers to its physical state and structure as a solid. The solid-state form is important because it can significantly impact the drug’s performance, including its solubility, stability, and bioavailability. During the manufacturing process, the solid-state form of a drug substance may change, potentially impacting the stability of the drug product(Zhou et al., 2024). Understanding and controlling the solid-state form is crucial in drug development to ensure consistent quality and efficacy.

**Particle size distribution:** Particle size distribution refers to the range and proportion of different particle sizes present in a sample. It is a critical parameter in pharmaceutical development as it can significantly influence the drug’s behavior and performance, including its dissolution rate, bioavailability, and stability. Ensuring a consistent particle size distribution is essential for maintaining the quality and efficacy of the drug product. Manufacturers often optimize the milling and granulation processes to achieve the desired particle size distribution. Understanding and controlling particle size distribution is crucial for developing high-quality pharmaceutical products that perform consistently and effectively.

**Hygroscopicity**: Hygroscopicity refers to the ability of a drug substance to absorb moisture from its surrounding environment. This characteristic is crucial in the pharmaceutical field as it can significantly impact the drug’s stability, manufacturing process, and overall performance. During formulation development, the hygroscopic nature of the drug substance must be considered to ensure product stability. Suitable excipients may be selected to stabilize the drug substance, and moisture-protective packaging might be employed. Understanding and managing the hygroscopicity of a drug substance is essential for maintaining the quality and efficacy of pharmaceutical products. It aids in designing formulations that remain stable and effective throughout their shelf life.

**Solubility:** Solubility is the capacity of a drug substance to dissolve in a solvent, typically water or other biological fluids. It is a crucial parameter in drug development because it affects the drug’s absorption, bioavailability, and overall effectiveness. Solubility can vary with changes in the pH of the medium and can be influenced by the presence of other compounds or excipients in the formulation. To measure solubility, an excess of the drug substance is added to a solvent and allowed to reach equilibrium. Analytical techniques such as High-Performance Liquid Chromatography (HPLC) or spectrophotometry are then used to quantify the dissolved drug. Solubility impacts the rate at which the drug dissolves in the gastrointestinal tract, influencing its absorption. Poorly soluble drugs may have limited bioavailability, necessitating formulation strategies to enhance solubility. Understanding solubility is essential for designing suitable dosage forms and selecting appropriate excipients. Techniques such as salt formation, particle size reduction(Khan et al., 2022), the use of solubilizing excipients(Karataş, Yüksel, & Baykara, 2005), and creating solid dispersions(Chiou & Riegelman, 1971; Sareen, Mathew, & Joseph, 2012) can be employed to improve the solubility of poorly soluble drugs.

**Moisture content:** It refers to the amount of water present in a drug substance. This property is crucial as it can impact the stability, quality, and performance of the drug product. It is typically measured using techniques such as Karl Fischer titration, thermogravimetric analysis (TGA), or loss on drying (LOD). High moisture content can lead to hydrolysis or degradation of the drug substance, reducing its potency and shelf life. It can also affect the physical properties of the drug, such as particle size, flowability, and compressibility. Drug substances with high moisture content may require special storage conditions to prevent moisture absorption. Desiccants and moisture-resistant packaging are commonly used to protect the drug substance from humidity. During formulation development, moisture content can Influence the manufacturing process, particularly operations like granulation and compression. Ensuring the appropriate moisture content in a drug substance is vital for maintaining its stability and efficacy.”

**Residual solvents:** They are the trace amounts of solvents that remain in a drug substance after the manufacturing process is complete. These solvents are typically used during synthesis, purification, or formulation stages and must be minimized to ensure the safety and quality of the drug product.

* **Class 1 Solvents**: Solvents to be avoided due to their toxicity (e.g., benzene).
* **Class 2 Solvents**: Solvents to be limited due to potential toxicity (e.g., methanol, acetonitrile).
* **Class 3 Solvents**: Solvents with low toxic potential that are less stringently regulated (e.g., ethanol).

Regulatory agencies, such as the International Council for Harmonisation (ICH), provide guidelines on acceptable levels of residual solvents in pharmaceutical products (ICH Q3C guidelines) (International Conference on Harmonisation of Technical Requirements for Registration Of Pharmaceuticals For Human Use, April 2021). These limits are based on safety assessments and are intended to minimize health risks. High levels of residual solvents can pose toxicity risks to patients and can also affect the stability, efficacy, and shelf life of the drug product.”

**Chemical stability:** It refers to a drug substance’s ability to maintain its chemical integrity and labeled potency within specified limits throughout its shelf life(Yadav, Yadav, & Mishra, 2023). This stability involves resistance to chemical changes such as degradation, oxidation, hydrolysis, and photolysis over time. Chemical instability can lead to reduced potency, formation of toxic degradation products, and alterations in the drug’s physical properties. Ensuring chemical stability is crucial for maintaining the drug’s efficacy and safety throughout its shelf life. Formulation strategies, such as using stabilizing excipients, optimizing pH, and employing antioxidants, can enhance chemical stability. Proper packaging, like airtight and light-resistant containers, protects the drug substance from environmental factors. Maintaining the chemical stability of a drug substance is vital for delivering safe and effective pharmaceutical products to patients.

**Flow properties:** It refers to how well a powder can move under specified conditions without clumping, sticking, or causing blockages in manufacturing equipment. Smaller particles may lead to poor flow due to increased surface area and cohesion. Irregularly shaped particles and rough surfaces can also hinder flow, while excess moisture can cause particles to stick together, reducing flowability. Powders with higher density generally exhibit better flow properties. Common techniques for assessing flow properties include the angle of repose, compressibility index (Carr’s index), and Hausner ratio(Sharma, Sharma, Deep, & Sharma). Good flow properties are essential for uniform mixing, accurate dosing, and consistent compression into tablets or filling into capsules. Understanding and optimizing the flow properties of a drug substance is crucial for ensuring efficient and consistent manufacturing of high-quality pharmaceutical products

Evaluate how each drug substance attribute might impact the drug product’s critical quality attributes (CQAs), including assay, degradation products, content uniformity, and dissolution. The relative risk of each attribute will be classified as high, medium, or low. High-risk attributes will need further investigation, while low-risk attributes will not require additional examination. Medium-risk attributes will be considered acceptable based on current knowledge, although further investigation may be necessary to mitigate the risk. The rationale behind the assigned risk levels should be detailed. Systematically evaluating and categorizing the risk of each attribute helps identify and address potential issues, thereby maintaining the quality and safety of the drug product.

Excipients, as the second component of the drug product, must be evaluated through an excipient compatibility study. Drug substance in a formulation comes into close contact with one or more excipients, there is a possibility of physical and/or chemical interactions. These interactions could negatively affect the physical properties, stability, or performance of the drug product(Crowley & Martini, 2001) (McDaid, Barker, Fitzpatrick, Petts, & Craig, 2003). Therefore, selecting the right excipients is crucial to avoid such negative effects and develop a robust and effective formulation (Makai, Bajdik, Erős, & Pintye-Hódi, 2008; Tiţa, Fuliaş, Bandur, Marian, & Tiţa, 2011; Tita, Jurca, Fulias, Marian, & Tita, 2013). Screening for excipient-API compatibility is a key aspect of formulation development. Furthermore, the USFDA’s 21st century current Good Manufacturing Practices (cGMP) initiative and the International Council on Harmonization (ICH) Q8 guidelines encourage pharmaceutical manufacturers to apply Quality by Design (QbD) principles in their drug development processes(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009). These guidelines emphasize the importance of understanding interactions between formulation components. Recent advances in both thermal and non-thermal analytical techniques have enhanced the efficiency of detecting, monitoring, and preventing incompatibilities early in the drug development process(Marini et al., 2003).

Drug excipient compatibility study should involve:

* A binary mixture of the drug substance and individual excipients, approximately in a 1:1 ratio.
* A mixture of the drug substance with all excipients.
* These mixtures should be stored in the solid state at 25°C/60% RH and 40°C/75% RH in both open and closed containers for one month.
* The assay and degradation products should then be checked to evaluate compatibility.

The excipient grade should be chosen based on the results of the excipient compatibility study. Additionally, excipient types identical to those in the RLD formulation should be selected for generic product development, provided there is no infringement on the brand product’s patent.

## Drug Product Development

In a QbD approach, the risk assessment tool aims to identify high-risk factors requiring detailed investigation and control. The results enable action plans to mitigate these risks, converting them into low-risk factors and minimizing threats to critical quality attributes(European Medicines Agency (EMA) - U.S. Food and Drug Administration (FDA), 2014; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, May 2023; Tomba, Facco, Bezzo, & Barolo, 2013). Conducting a risk assessment of critical material attributes (CMAs) and critical process parameters (CPPs) should be performed before initiating formulation and process development. This should be followed by optimizing the formulation and process using a design of experiment (DOE) in which design space to be identified. Sequence of QbD approach shown in **Figure 1**.

**A diagram of a design process

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**Figure 1 : Sequence of QbD approach**

Conducting a risk assessment of critical material attributes and critical process parameters should be performed before initiating formulation and process development. This should be followed by optimizing the formulation and process using a design of experiment (Chowdary & Shankar, 2016; N. Politis, Colombo, Colombo, & M. Rekkas, 2017), known as design space development, and establishing a control strategy.

Critical Material Attribute (CMA) : A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material (Maguire & Peng, 2015).

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, August 2009).

Design space means multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

## Formulation Development

A risk assessment of formulation variables, e.g. drug substance particle size distribution, disintegrant level, glidant level, diluent level, binder level, and lubricant level to be conducted to evaluate the potential impact of each attribute on drug product CQAs, such as assay, degradation product, content uniformity, and dissolution. In the relative risk of each attribute to be categorized as high, medium, or low. High-risk attributes will require further investigation, while low-risk attributes will not need additional examination. Medium-risk attributes will be considered acceptable based on current knowledge, although further investigation may be needed to mitigate the risk. The justification behind the assigned risk level to be explained in detail. In **Table 1** below, the initial risk assessment of the formulation variables is presented for illustrative purposes only.

**Table 1 : Initial risk assessment of the formulation variables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug product CQA** | **Formulation Variables** | | | |
| **Variable # 1** | **Variable # 2** | **Variable # 3** | **Variable # 4** |
| Assay | High | Medium | Low | Low |
| Content uniformity | High | High | Low | Low |
| Dissolution | Low | Low | Low | High |
| Degradation products | Low | Low | Low | Low |

Formulation development to be focused on evaluation of the high-risk formulation variables identified in the initial risk assessment. Initial formulation development study to be conducted at laboratory scale (Approximately 1.0 kg to 3.0 kg based on available equipment). During initial formulation development, standard manufacturing process is to be used (Process parameters do not require to be optimized during this time). Analyzing the impact of a single factor at a time is not only labor-intensive but often unproductive. Instead, one should consider multiple factors (independent variables) simultaneously in various settings through different experiments, observing their effects on the output or response (dependent variable). This approach is a more efficient and effective method for conducting or simulating experiments (Chakraborty, 2023). Design of experiment which will include formulation variables at different levels to be used to evaluate combinations effect of formulation variables on drug product critical quality attributes as well as in-process quality tests e.g. Hardness, friability, disintegration time. In **Table 2** below, the optimization design for three formulation variables (classified as high or medium risk) is presented at two different levels using a 23 factorial design, including one center point level for each formulation variable trial in replication. Meanwhile, **Table 3** showcases the number of trials and experimental results of the design for illustrative purposes only.

All tables in this review article are presented solely for illustrative purposes. For further details, please refer to following example Quality by design for ANDA: An example for Immediate-release dosage form (U.S. Food and Drug Administration (FDA), April 2012) and An example of Modified Release dosage form(U.S. Food and Drug Administration (FDA), December 2011).

**Table 2 : Design of 23 full factorial DOE to study formulation variable**

|  |  |  |
| --- | --- | --- |
| **Factors:**  **Formulation Variables** | **Level** | |
| **-1** | **1** |
| Variable 1 | Low | High |
| Variable 2 | Low | High |
| Variable 4 | Low | High |
| **Response** | **Target** | |
| Response 1 | \* | |
| Response 2 | \* | |
| Response 3 | \* | |
| Response 4 | \* | |

\* Record value

**Table 3 : Trials and experimental results of the design**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Factors: Formulation Variables** | | | **Responses** | | | |
| **Variable 1 level** | **Variable 2 level** | **Variable 3 level** | **Response 1** | **Response 2** | **Response 3** | **Response 4** |
|  | Low | Low | Low | **\*** | **\*** | **\*** | **\*** |
|  | Low | Low | High | **\*** | **\*** | **\*** | **\*** |
|  | Low | High | Low | **\*** | **\*** | **\*** | **\*** |
|  | Low | High | High | **\*** | **\*** | **\*** | **\*** |
|  | High | Low | Low | **\*** | **\*** | **\*** | **\*** |
|  | High | Low | High | **\*** | **\*** | **\*** | **\*** |
|  | High | High | Low | **\*** | **\*** | **\*** | **\*** |
|  | High | High | High | **\*** | **\*** | **\*** | **\*** |
|  | Middle | Middle | Middle | **\*** | **\*** | **\*** | **\*** |
|  | Middle | Middle | Middle | **\*** | **\*** | **\*** | **\*** |
|  | Middle | Middle | Middle | **\*** | **\*** | **\*** | **\*** |

\* Record value

Acceptable ranges for high and medium risk formulation variables to be established during formulation development optimization and to be included in the control strategy. Additionally, risk assessment of the formulation variables will be updated with justification as shown in **Table 4**.

**Table 4 : Updated risk assessment of the formulation variables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug product CQA** | **Formulation Variables** | | | |
| **Variable # 1** | **Variable # 2** | **Variable # 3** | **Variable # 4** |
| CQA 1 | Low | Low | Low | Low |
| CQA 2 | Low | Low | Low | Low |
| CQA 3 | Low | Low | Low | Low |
| CQA 4 | Low | Low | Low | Low |

Following the intensive application of factorial design during formulation development, a tentative composition of the generic product will be selected for optimizing the manufacturing process.

## Drug Product Manufacturing Process Development

Prior to starting the manufacturing process, a process map for the finalized formulation will be established. Each step in the manufacturing process will be listed in the order of occurrence. This map will illustrate the material attributes and process parameters that can potentially impact the quality attributes of intermediate and finished products. The material attributes of the input materials and the process parameters used at the initial step determine the quality attributes of the output material (intermediate) produced at this step. The material attributes of the intermediate from this step and the process parameters of the subsequent step in the manufacturing process will determine the quality attributes of the next intermediate and, eventually, the finished drug product. This cycle continues until the final step, where the finished drug product is manufactured, and its quality attributes are evaluated. The process map will guide the risk assessments performed during process development.

A group of white rectangular labels

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**Figure 2 : Process Map Illustration**

A risk assessment of overall manufacturing process, e.g. granulation (dry or wet), milling, blending, lubrication and compression to be conducted to evaluate the potential impact of each attribute on drug product CQAs, such as assay, degradation product, content uniformity, and dissolution. In addition to the overall manufacturing process, each variable in the manufacturing process will be evaluated for risk assessment. The relative risk of each attribute will be categorized as high, medium, or low. High-risk attributes will require further investigation, while low-risk attributes will not need additional examination. Medium-risk attributes will be considered acceptable based on current knowledge, although further investigation may be needed to mitigate the risk. The justification behind the assigned risk level to be explained in detail. In **Table 5** below, the initial risk assessment of the formulation variables is presented for illustrative purposes only.

**Table 5 : Initial risk assessment of the overall manufacturing variables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug product CQA** | **Manufacturing Process Variables** | | | |
| **Process # A** | **Process # B** | **Process # C** | **Process # D** |
| CQA 1 | High | Medium | Low | Low |
| CQA 2 | High | High | Low | High |
| CQA 3 | Low | Low | High | High |
| CQA 4 | Low | Low | Low | Low |

Manufacturing process development to be focused on evaluation of the high-risk process variables identified in the initial risk assessment.

Design of experiment which will include manufacturing process variables at different levels to be used to evaluate combinations effect of process variables on drug product quality attributes of output materials as mentioned in process map. This assessment will continue through to the final steps of the manufacturing process, where the quality attributes of the finished product will be evaluated. In **Table 6** below, three variables for Manufacturing Process # A is presented at two different levels using a 23-1 fractional factorial design with one center point where number of run can be minimized. **Table 7** showcases the number of trials and experimental results of the design for manufacturing process # 1 for illustrative purposes only.

**Table 6 : Design of 23-1 to study Manufacturing Process # A**

|  |  |  |
| --- | --- | --- |
| **Factors:**  **Manufacturing Process Variables** | **Level** | |
| **-1** | **1** |
| Variable 1 | Low | High |
| Variable 2 | Low | High |
| Variable 3 | Low | High |
| **Response** | **Target** | |
| Response 1 | \* | |
| Response 2 | \* | |

\* Record value

**Table 7 : Trials and experimental results of the design for Manufacturing Process # A**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial** | **Factors: Manufacturing Process Variables** | | | **Responses** | |
| **Variable 1 level** | **Variable 2 level** | **Variable 3 level** | **Response 1** | **Response 2** |
|  | Low | Low | High | **\*** | **\*** |
|  | High | Low | Low | **\*** | **\*** |
|  | Low | High | Low | **\*** | **\*** |
|  | High | High | High | **\*** | **\*** |
|  | Middle | Middle | Middle | **\*** | **\*** |

\* Record value

Similar to Manufacturing Process # A, all other manufacturing processes will be optimized using design of experiments.

Acceptable ranges for high and medium risk manufacturing process variables to be established during process development optimization and to be included in the control strategy. Additionally, risk assessment of each process variables will be updated with justification.

**Table 8 : Updated risk assessment of the Manufacturing process variables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug product CQA** | **Manufacturing Process Variables** | | | |
| **Variable # 1** | **Variable # 2** | **Variable # 3** | **Variable # 4** |
| CQA 1 | Low | Low | Low | Low |
| CQA 2 | Low | Low | Low | Low |
| CQA 3 | Low | Low | Low | Low |
| CQA 4 | Low | Low | Low | Low |

## Scale-Up from Lab to Pilot Scale and Commercial Scale

After the formulation and process are optimized at the lab scale, they are scaled up to pilot and commercial production. Various scale-up principles and mathematical equations are employed to facilitate the manufacturing process scale-up. For instance, wet granulation(Alves, Simões, Simões, & Gomes, 2024), roller compaction (Nesarikar et al., 2012), final lubrication blending(Kushner IV & Moore, 2010), tablet compression press speed scale up (Dumpala, Bhavsar, & Patil, 2020) and tablet coating scale up (Pandey, Turton, Joshi, Hammerman, & Ergun, 2006) all utilize specific scale-up principles and mathematical equations.

## Control Strategy

The control strategy is “a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (U.S. Food and Drug Administration (FDA), April 2009).

The control strategy will be developed from comprehensive studies on product and process understanding. These studies will investigate material attributes and process parameters that pose high risks to the CQAs of the drug product during the initial risk assessment. Variables with medium risk levels will also be evaluated in some instances. By systematically examining these factors, CMAs and CPPs will be identified, and acceptable operational ranges will be established. All variables deemed high risk in the initial risk assessment will be included in the control strategy, as the experimental conclusions will depend on the range(s) studied and the complex multivariate relationships between variables. This control strategy will thus provide a comprehensive overview of quality assurance based on current process and product knowledge. The strategy may be refined further based on experiences gained during the commercial lifecycle of the product. However, any post-approval modifications will be reported to the agency in line with CFR 314.70 and will follow guidelines for scale-up and post-approval changes.

The control strategy should encompass the critical material attributes of both drug substances and excipients, in-process controls, high-risk process parameter ranges to be investigated during development, proposed operating ranges for commercial manufacturing, and finished product release specifications.

**Table 9 : Control strategy example**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Factor** | **Attributes or Parameters** | **Range study**  **(Lab scale)** | **Set point for Pilot batch** | **Set point for verification batch (Commercial scale)** | **Proposed range for commercial scale** | **Purpose of control** |
| Raw material attributes | | | | | | |
| API | CMA 1 | \* | \* | \* | \* | \* |
| CMA 2 | \* | \* | \* | \* | \* |
| Excipient 1 | CMA | \* | \* | \* | \* | \* |
| Excipient 2 | CMA 1 | \* | \* | \* | \* | \* |
| CMA 2 | \* | \* | \* | \* | \* |
| Excipient 3 | CMA | \* | \* | \* | \* | \* |
| Excipient 4 | CMA | \* | \* | \* | \* | \* |
| Manufacturing Process # A | | | | | | |
| Process step | CPP 1 | \* | \* | \* | \* | \* |
| CPP 2 | \* | \* | \* | \* | \* |
| CPP 3 | \* | \* | \* | \* | \* |
| Manufacturing Process # A In-Process specification | | | | | | |
| Manufacturing Process # B | | | | | | |
| Process step | CPP 1 | \* | \* | \* | \* | \* |
| CPP 2 | \* | \* | \* | \* | \* |
| Manufacturing Process # B In-Process specification | | | | | | |
| Manufacturing Process # C | | | | | | |
|  | CPP 1 | \* | \* | \* | \* | \* |
| Process step | CPP 2 | \* | \* | \* | \* | \* |
|  | CPP 3 | \* | \* | \* | \* | \* |
| Manufacturing Process # C In-Process specification | | | | | | |

\* Record value

**Table 10 : Finished product release specification**

|  |  |
| --- | --- |
| **Test** | **Acceptance criteria** |
| Test A | \* |
| Test B | \* |
| Test C | \* |
| Test D | \* |

\* Record value

## Product Lifecycle Management and Continual Improvement

Once approved, the manufacturing process for the generic dosage form will be validated using a lifecycle approach that incorporates risk-based decision-making throughout the drug product lifecycle, as outlined in the FDA's process validation guidance(U.S. Food and Drug Administration (FDA), January 2011).

The concept of validation was initially introduced by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid-1970s with the aim of enhancing pharmaceutical quality. Its primary objective is to ensure that quality is integrated into the system at every stage, rather than being assessed solely at the final step(Anju & Pandey, 2017). This concept underwent further development in the United States in 1978.

The QbD approach to be adopted during the pharmaceutical development of the generic dosage form that will support product and process understanding aligned with Stage 1 (Process Design) of process validation. In Stage 1, the commercial manufacturing process will be defined based on knowledge acquired during development and scale-up activities, and control strategy will be established. The objective of Stage 2 (Process Qualification) will be to confirm the process’s ability to achieve reproducible commercial manufacturing. The manufacturing facility will be designed in compliance with cGMP regulations for Buildings and Facilities(USFDA). Activities will be undertaken to verify that utilities and equipment are fit for their intended purpose and function correctly. The process performance qualification (PPQ) protocol will be drafted, reviewed, approved, and executed to demonstrate that the commercial manufacturing process operates as intended. The objective of Stage 3 (Continued Process Verification) will be to ensure the process consistently remains in a state of control (the validated state) during commercial production. Stage 3 may be best classified into Stage 3a (Data Collection and Monitoring During Routine Production) emphasis on collecting data during routine production to ensure the validated process remains in control and capable of consistently producing products of the desired quality. It mainly focuses on early routine production batches where more intensive data collection and monitoring may be performed to confirm the process is stable post-validation whereas Stage 3b (Ongoing Process Verification) emphasis on the long-term, ongoing verification of the process throughout the lifecycle of the product (Pazhayattil et al., 2018). Process validation cycle illustrated in the **Figure 3**.

A diagram of process

Description automatically generated

**Figure 3 : Process Validation Cycle**

As part of ongoing process verification, the performance of the manufacturing process will be continuously monitored throughout the product's lifecycle to ensure it operates as expected and delivers the desired quality attributes. Statistical techniques will be employed to measure and assess process performance and capability. If any unexpected variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future issues, ensuring the process remains under control. Furthermore, insights gained during routine manufacturing will be used to adjust process parameters, contributing to the ongoing improvement of the drug product.

Following recommendations by the FDA and EMA (QbD), a design space is determined early in product development through pilot-scale experiments. The commercial process is carried out within a specific area of this design space, known as the Normal Operating Range (NOR), which is close to the target operating conditions. The NOR for a commercial process is established after assessing potential scale-up effects. Continuous Process Verification takes place within the NOR. Additionally, the continuous monitoring plan for quality attributes and/or process parameters, as part of the routine control strategy, will further enhance a QbD-based product submission (Alsmeyer & Pazhayattil, 2014).

# CONCLUSION

The implementation of Quality by Design (QbD) in the development of generic solid oral drug products represents a paradigm shift in pharmaceutical manufacturing and quality assurance. By leveraging a systematic, scientific, and risk-based approach, QbD enables a deeper understanding of product and process characteristics, ensuring consistent quality while meeting regulatory expectations. The integration of key elements, such as critical quality attributes (CQAs), critical process parameters (CPPs), and design space, empowers manufacturers to achieve robust processes with reduced variability. Additionally, regulatory guidance, including ICH Q8(R2) through ICH Q14, has provided a clear framework to support practical adoption.

Although challenges persist, such as the need for specialized expertise and resource allocation, the benefits of QbD—enhanced product quality, optimized processes, and greater regulatory flexibility—are undeniable. As industry continues to evolve, the broader adoption of QbD principles will further elevate the standards of generic drug development, ultimately benefiting both manufacturers and patients through improved access to high-quality medicines.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

**CONSENT AND ETHICAL APPROVAL**

Not applicable

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